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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/43, 31/395</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/09042</b> <b>(43) International Publication Date:</b> 13 March 1997 (13.03.97)
<b>(21) International Application Number:</b> PCT/US96/14554 <b>(22) International Filing Date:</b> 5 September 1996 (05.09.96) <b>(30) Priority Data:</b> 60/003,353 7 September 1995 (07.09.95) US <b>(71) Applicant (for all designated States except US):</b> SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> BURCH, Daniel, Joseph [US/US]; 1250 South Collegeville Road, P.O. Box 5089, Collegeville, PA 19426-0989 (US). <b>(74) Agents:</b> WILLIAMS, Janice, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).		<b>(81) Designated States:</b> AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PHARMACEUTICAL FORMULATION  <b>(57) Abstract</b>  Pharmaceutical formulations comprising amoxycillin and clavulanate in a ratio of from 10:1 to 20:1 are of use in the empiric treatment of infections potentially caused by DRSP.		

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### Pharmaceutical Formulation

This invention relates to pharmaceutical formulations comprising amoxycillin and a salt of clavulanic acid (hereinafter termed "clavulanate" unless a specific salt is identified).

The combination of amoxycillin and clavulanate is an effective empirical treatment for bacterial infections and may be administered by oral dosing, for instance in the form of tablets, and, for paediatric formulations, aqueous solutions or suspensions, typically as a flavoured syrup.

Clavulanate is a  $\beta$ -lactamase inhibitor and is included with the  $\beta$ -lactam antibiotic amoxycillin to counter a  $\beta$ -lactamase mediated resistance mechanism. Some microorganisms such as *Streptococcus pneumoniae* have resistance mechanisms which are not  $\beta$ -lactamase mediated. WO94/16696 discloses generally that potassium clavulanate may enhance the effectiveness of beta-lactam antibiotics such as amoxycillin against microorganisms having a resistance mechanism which is not  $\beta$ -lactamase mediated.

*Streptococcus pneumoniae* is an important pathogen in respiratory tract infection in the community. *S pneumoniae* is the most commonly implicated bacterium in the important respiratory tract infections of otitis media in paediatrics and sinusitis in patients of all ages and acute exacerbations of bronchitis and pneumococcal pneumonia in adults. There have been increasing reports in Europe and the US of the emergence of DRSP (drug-resistant *Streptococcus pneumoniae*) with decreased susceptibility to  $\beta$ -lactam and other antibiotics.

Whilst confirmed cases of DRSP infection may be successfully treated with relatively high levels of amoxycillin, there still remains the need to develop effective empiric treatments, where DRSP may be suspected, for instance in an area with a high prevalence of DRSP, but where other,  $\beta$ -lactamase producing, organisms may also be present.

It has now been found that empiric treatment of infections potentially caused by DRSP may be successfully treated with formulations of co-amoxiclav which have a relatively large amount of amoxycillin.

Accordingly, the present invention provides a pharmaceutical formulation adapted for oral administration comprising amoxycillin and clavulanate in a weight ratio between 10:1 and 20:1 inclusive in combination with a pharmaceutically acceptable carrier or excipient.

Such formulations are of use for the empiric treatment of infections, potentially caused by DRSP, in particular respiratory tract infections such as otitis

media in paediatrics and sinusitis in patients of all ages and acute exacerbations of bronchitis and pneumococcal pneumonia in adults

The invention also provides for the use of amoxycillin and clavulanate in a ratio of between 10:1 and 20:1 inclusive in the manufacture of a medicament for oral administration for the empiric treatment of infections potentially caused by DRSP in human patients.

The invention also provides a method for the empiric treatment of infections potentially caused by DRSP in a human patient comprising the oral administration to a patient in need thereof of a pharmaceutical formulation comprising amoxycillin and clavulanate in a weight ratio between 10:1 and 20:1 inclusive.

The formulations of the present invention are suitable for use with patients of all ages, including adult, older children and paediatric patients.

The weight ratios of amoxycillin:clavulanate expressed herein are as free acid equivalent. Preferred amoxycillin:clavulanate ratios are between 12:1 to 16:1 inclusive, especially about  $14:1 \pm 5\%$ .

In the formulations of the invention the amoxycillin is preferably in the form of amoxycillin trihydrate, although sodium amoxycillin, for example the crystalline form of sodium amoxycillin which is disclosed in EP 0131147 A may also be used.

Clavulanate is preferably in the form of potassium clavulanate. Potassium clavulanate is extremely moisture-sensitive and should be stored and handled in conditions of 30% RH or less, ideally as low as possible. Solid dosage forms should be packaged in atmospheric moisture-proof containers, and such forms and/or their containers may contain a desiccant.

The formulations of the invention may be made up into solid dosage forms for oral administration by a method conventional to the art of pharmaceutical technology, e.g. tablets or powder or granular products for reconstitution into a suspension or solution. Suitable ingredients and suitable methods for making such tablets are disclosed in for example GB 2 005 538-A, WO 92/19227 and WO 95/28927. Powder or granular formulations, such as paediatric suspension formulations, may be manufactured using techniques which are generally conventional in the field of manufacture of pharmaceutical formulations and in the manufacture of dry formulations for reconstitution into such suspensions. For example a suitable technique is that of mixing dry powdered or granulated ingredients for loading into a suitable container.

For paediatric dosing, the formulations of the invention are preferably made up into a sweet flavoured aqueous syrup formulation of generally conventional formulation (except for its novel amoxycillin : clavulanate ratio and intended use) containing a suitable weight of the amoxycillin and clavulanate in a unit dose volume,

e.g. 5 ml or 2.5 ml of the syrup. Because of the water-sensitivity of clavulanate it is preferred to provide such a syrup formulation as dry powder or granules contained in an atmospheric moisture-proof container or sachet for make up with water or other suitable aqueous medium shortly prior to use.

5       The formulation of this invention will normally, in addition to its active materials amoxycillin trihydrate and potassium clavulanate, also include excipients which are standard in the field of formulations for oral dosing and used in generally standard proportions, and at generally standard particle sizes and grades etc.

10       In the case of paediatric oral suspensions, these excipients may comprise suspending aids, glidants (to aid filling), diluents, bulking agent, flavours, sweeteners, stabilisers, and in the case of dry formulations for make up to an aqueous suspension, an edible desiccant to assist preservation of the potassium clavulanate against hydrolysis by atmospheric moisture on storage. Potassium clavulanate is normally supplied in admixture with silicon dioxide as diluent.

15       Suitable excipients for use include xantham gum (suspension aid), colloidal silica (glidant), succinic acid (stabiliser), aspartame (sweetener), hydroxypropyl-methylcellulose (suspension aid) and silicon dioxide (desiccant, diluent for potassium clavulanate and bulking agent). Flavours may comprise common flavours such as orange, banana, raspberry and golden syrup, or mixtures thereof, to suit local  
20 requirements.

      Generally the proportion of active materials amoxycillin trihydrate and potassium clavulanate in a dry formulation for make up with aqueous media into a solution, suspension or syrup formulation of the invention may be around 30-80 wt%.

25       The present invention therefore also provides a process for manufacture of a formulation as described above.

      The formulations of the invention may be adapted to paediatric dosing, i.e. to patients aged between 3 months to 12 years. Such formulations may be dosed in daily quantities up to the maximum normal permitted dose of amoxycillin and clavulanate.

30       A suitable dosage quantity of the formulation of the invention for paediatric patients is 75 to 115 mg/kg amoxycillin per day and 5 to 7.5 mg/kg of clavulanate per day. Suitably, the dosage is administered bid, for example in two, preferably equal, unit doses per day, suitably around 12 hours apart. A suitable dosage for use in such a regimen is  $90 \pm 10\%$ , especially  $\pm 5\%$ , mg/kg amoxycillin and  $6.4 \pm 10\%$ , especially  $\pm$   
35 5%, mg/kg clavulanate (i.e. nominally a 14:1 ratio) per day.

      Suitably, paediatric formulations as hereinbefore described are provided which comprise from 500 to 700, preferably about 600mg of amoxycillin/5ml of

formulation when reconstituted and from 35 to 50 mg, preferably about 43mg of clavulanic acid/5ml of formulation when reconstituted.

For older children and adult patients these quantities may be increased *pro rata*. A suitable dosage for use in such a regimen is  $3500 \pm 10\%$ , especially  $\pm 5\%$ , mg amoxycillin and  $250 \pm 10\%$ , especially  $\pm 5\%$ , mg clavulanate (i.e. nominally a 14:1 ratio) per day, preferably administered bid, for example in two, preferably equal, unit doses per day, suitably around 12 hours apart

The formulation of the invention may for example be provided in solid unit dose forms embodying suitable quantities for the administration of such a daily dose. For example a unit dosage form may be tablets, or sachets containing granules or powders for reconstitution, one or two of which are to be taken at each bid dosing interval. Alternatively a unit dose may be provided as a bulk of solid or solution or suspension, e.g. as a syrup for paediatric administration, together with a suitable measuring device of known type to facilitate administration of a suitable unit dose quantity of the formulation. A suitable unit dose quantity is one which enables the administration of the above-mentioned daily dosage quantity divided between two bid doses.

For paediatric patients, a suitable unit dose quantity is preferably one which enables the administration of the above-mentioned daily dosage quantity, divided between two bid doses, e.g. half of the above-mentioned daily dose, in a volume of a solution or suspension suitable for oral administration to a paediatric patient, preferably of between 2.5 to 10 ml, preferably as a syrup. A paediatric formulation may therefore comprise a bulk of a solution or suspension, e.g. a syrup, or granules or powder which can be made up into such a solution or suspension, at a concentration of solution or suspension which contains such a dose in such a volume.

The present invention therefore also provides the above described formulation provided for administration in such doses.

For adults, a suitable unit dose may be provided in a tablet. Suitably, for a bid dosage regimen based on 1750mg amoxycillin/125mg clavulanate per unit dose, this may conveniently be provided as two tablets, one comprising amoxycillin and clavulanate and a second comprising amoxycillin alone. Accordingly, in a further aspect, the present invention provides for a unit dosage of 1750mg amoxycillin and 125mg clavulanate provided by two tablets, one comprising 875mg amoxycillin and 125mg clavulanate and a second comprising 875mg amoxycillin. A suitable tablet comprising 875mg amoxycillin and 125mg clavulanate is marketed by SmithKline Beecham in several countries and is also described in WO 95/28927 (SmithKline Beecham).

The invention will now be described by way of example only with reference to Figs. 1, 2 and 3 which show graphically the results of Example 3 below.

Figs. 1, 2 and 3 show respectively Log<sub>10</sub> of colony forming units ("cfu") of *S. Pneumoniae* strains N1387, 14319 and 410101 per lungs observed in rats following dosing with an amoxycillin : potassium clavulanate ("AMX : CA") formulation of this invention administered at 45 : 3.2 mg/kg amoxycillin : clavulanic acid equivalent, a comparison formulation administered at 22.5 : 3.2 mg/kg, and a non-treated control ("NTC") as described below.

**Example 1 - Paediatric formulation**

The following paediatric formulation comprising 600mg amoxicillin and 42.9mg clavulanic acid in 5ml of suspension when reconstituted:

5

<b>Ingredient</b>	<b>Quantity (mg)</b>
Amoxycillin trihydrate	697.00*
(equivalent to amoxicillin free acid)	600.00
Potassium Clavulanate/Syloid 1:1 blend	113.00**
(equivalent to clavulanic acid, including 8% overage)	46.332
Xanthan Gum	12.500
Aspartame	12.500
Succinic acid	0.835
Colloidal silicon dioxide	25.00
Hydroxypropyl methyl cellulose	79.650
Flavours	72.500
Silicon dioxide	86.315***
<b>Total fill weight</b>	<b>1100.00</b>

\* based on 86% potency as amoxicillin free acid

\*\* based on 41% potency as clavulanic acid in potassium clavulanate/Syloid 1:1 blend, including an 8% overage

\*\*\* quantity of silicon dioxide (Syloid) varies, according to quantities of amoxycillin trihydrate and potassium clavulanate/Syloid blend, such that total fill weight remains constant at 1100.00mg

Bottles are filled with 23.92g of formulated powder and then reconstituted with 84 ml of water immediately prior to use, to give 100ml of suspension.

10

**Example 2 - Tablet Formulation**

A tablet formulation comprising 875mg amoxycillin and 125mg clavulanate was prepared having the following composition:

<b>Ingredient</b>	<b>(mg.)</b>	<b>wt. %</b>
<b>Active Constituents:</b>		
Amoxycillin trihydrate	1017.4	70.2
(equivalent to amoxycillin)	875.00	
Potassium clavulanate	152.45	10.5
(equivalent to clavulanic acid)	125.0	
<b>Other Constituents:</b>		
Magnesium Stearate	14.50	1.00
Sodium Starch Glycollate	29.00	2.00
Colloidal Silicon Dioxide	10.0	0.70
Microcrystalline Cellulose	226.65	15.6
<b>Core tablet weight</b>	<b>1450.00</b>	<b>100.00</b>

5 The tablets are made by blending the amoxycillin, potassium clavulanate, and portions of microcrystalline cellulose and magnesium stearate, roller compacting this blend, then blending with the other constituents, before tableting on a conventional tablet press and coating. The tablet core is coated with a film (Opadry White YS-1-7700/Opadry White OY-S-7300 ex Colorcon) from an aqueous solvent system, to give tablets with a nominal coated weight of 1482mg. Further details of how the tablets are manufactured are provided in WO 95/28927 (SmithKline Beecham).

10 Similar tablets can be made in which the roller compaction step is replaced by slugging and /or a final film coating is applied from an organic solvent system such as dichloromethane rather than an aqueous solvent system.

15 A tablet formulation comprising 875mg amoxycillin was prepared having the following composition:

<b>Core components (mg/tablet)</b>		
	Amoxicillin trihydrate	1017.4 (875 fa)
	Crospovidone, NF	30.5
	Microcrystalline cellulose, NF	204.4
5	Sodium starch glycollate, NF	26.0
	Colloidal Silicon Dioxide, NF	8.7
	Magnesium stearate, NF	13.0
<b>Film Coat</b>		
10	Opadry Pink	39.0

The tablets are made by blending the amoxycillin and portions of microcrystalline cellulose and magnesium stearate, roller compacting this blend, then blending with the other constituents, before tableting on a conventional tablet press and coating.

15

### **Example 3 - Biological Data - In vivo Rat model:**

#### **Methodology.**

Animals were anaesthetised and the external jugular vein was cannulated for administration of compounds. At least 48h later animals were infected by intra-bronchial instillation of a 50 microlitre inoculum of *S Pneumoniae* by non surgical intubation. Inocula were prepared in cooled molten nutrient agar with a final inoculum of approximately  $10^6$ cfu in 50 microlitres of agar.

Dosing commenced 24h after infection and compounds were administered as a continuous infusion into the jugular vein designed to simulate in rat plasma the concentration versus time curves obtained in human serum following oral administration of amoxycillin / clavulanate. For each organism tested, three groups of animals were used. The first two groups received amoxycillin and clavulanate to simulate bid dosing of this combination at either 22.5/3.2 mg/kg (a 7:1 ratio) or 45/3.2 mg/kg (a 14:1 ratio) to children. The remaining group received an infusion of saline at a rate similar to the dosed groups and acted as infected non-treated controls. Dosing continued for 2-5 days, and 14 days after therapy ended the animals were killed and lungs removed aseptically for bacteriological assessment.

#### **Results**

Table 1 shows the MIC's of amoxycillin, amoxycillin:clavulanate and penicillin G for the three resistant strains of *S Pneumoniae* tested.

Table 1.

	Strain	MIC(mcg/ml)		Penicillin G
		Amoxycillin	Amox:clav.	
5	N1387	2	2	2 (R)
	14319	4	4	8 (R)
	410101	4	4	4 (R)

***Streptococcus Pneumoniae* N1387:**

Bacterial numbers in the lungs of saline-treated animals were  $6.97 \pm 0.30 \log_{10}$  cfu/lungs. Both doses of amoxycillin : clavulanate reduced the numbers of viable bacteria in the lungs significantly compared with control animals ( $4.37 \pm 0.93 \log_{10}$  cfu/lungs and  $2.62 \pm 0.85 \log_{10}$  cfu/lungs for the 7 : 1 and 14 : 1 ratios respectively;  $p < 0.01$ ). However as shown in Fig. 1 amoxycillin : clavulanate at the 14 : 1 bid ratio was significantly more effective than when administered at the lower ratio of 7:1.

***Streptococcus Pneumoniae* 14319:**

Bacterial numbers in the lungs of saline-treated animals were  $6.8 \pm 0.62 \log_{10}$  cfu/lungs. Amoxycillin : clavulanate at the 7:1 ratio reduced the numbers of viable bacteria in the lungs ( $6.26 \pm 0.47 \log_{10}$  cfu/lungs) but this reduction did not reach significance compared with control animals. However as shown in Fig. 2 amoxycillin : clavulanate at the 14 : 1 ratio bid reduced the bacterial count to  $4.28 \pm 0.82 \log_{10}$  cfu/lungs such that this dose was significantly more effective than control animals and animals treated with the lower ratio of 7:1.

***Streptococcus Pneumoniae* 410101.**

Bacterial numbers in the lungs of saline-treated animals were  $7.11 \pm 0.45 \log_{10}$  cfu/lungs. Amoxycillin : clavulanate at the 7:1 ratio reduced the numbers of viable bacteria in the lungs ( $6.14 \pm 0.6 \log_{10}$  cfu/lungs) significantly compared with control animals ( $p, 0.05$ ). However as shown in Fig. 3 amoxycillin : clavulanate at the 14 : 1 ratio bid reduced the counts to  $3.91 \pm 0.81 \log_{10}$  cfu/lungs and was significantly more effective than animals treated with the lower ratio of 7:1.

**Claims**

1. A pharmaceutical formulation comprising amoxycillin and clavulanate in a weight ratio between 10 : 1 and 20 : 1 inclusive.  
5
2. A formulation as claimed in claim 1 in which the ratio of amoxycillin to clavulanate is between 12 : 1 and 16 : 1 inclusive.
3. A formulation as claimed in claim 1 in which the ratio of amoxycillin to clavulanate is about 14 : 1.  
10
4. A formulation as claimed in any one of claims 1 to 3 in which amoxycillin is in the form of amoxycillin trihydrate.
5. A formulation as claimed in any one of claims 1 to 4 in which clavulanate is in the form of potassium clavulanate.  
15
6. A formulation as claimed in any one of claims 1 to 5 adapted for administration to paediatric patients in the form of a powder or granular product for reconstitution into a suspension or solution and which comprises from 500 to 700mg/5ml of amoxycillin and from 35 to 50mg/5ml of clavulanate when reconstituted.  
20
7. A formulation as claimed in any one of claims 1 to 5 in the form of tablets and adapted to provide about 1750mg amoxycillin and 125mg clavulanate per unit dose.  
25
8. A formulation as claimed in claim 7 comprising a first tablet comprising 875mg amoxycillin and 125mg clavulanate and a second tablet comprising 875mg amoxycillin.
9. A process for preparing a pharmaceutical formulation according to any one of the preceding claims which process comprises admixing the ingredients thereof in any order that is convenient.  
30
10. The use of amoxycillin and clavulanate in a ratio of between 10:1 and 20:1 inclusive in the manufacture of a medicament for oral administration for the empiric treatment of infections potentially caused by DRSP in human patients.  
35

11. A method for the empiric treatment of infections potentially caused by DRSP in a human patient comprising the oral administration to a patient in need thereof of a pharmaceutical formulation comprising amoxycillin and clavulanate in a weight ratio between 10:1 and 20:1 inclusive.
- 5
12. A method as claimed in claim 11 in which the dosage quantity for paediatric patients is 75 to 115 mg/kg amoxycillin per day and from 5 to 7.5 mg/kg of clavulanate per day.
- 10
13. A method as claimed in claim 12 in which the dosage quantity is  $90 \pm 10\%$  mg/kg amoxycillin and  $6.4 \pm 10\%$  mg/kg clavulanate.
14. A method as claimed in claim 11 in which the dosage amount for an older child or an adult patient is  $3500 \pm 10\%$  mg amoxycillin and  $250 \pm 10\%$  mg clavulanate.
- 15
15. A method as claimed in claim 13 or claim 14 in which the dosage is administered bid.

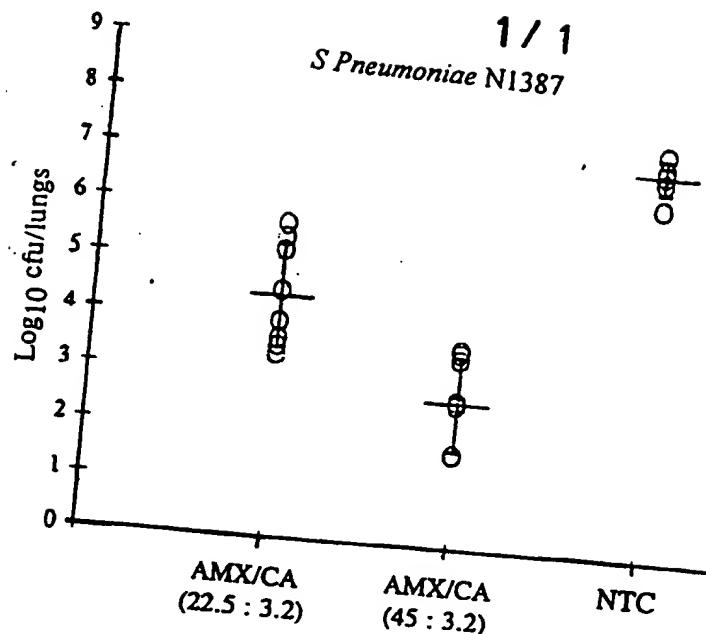


Fig. 1

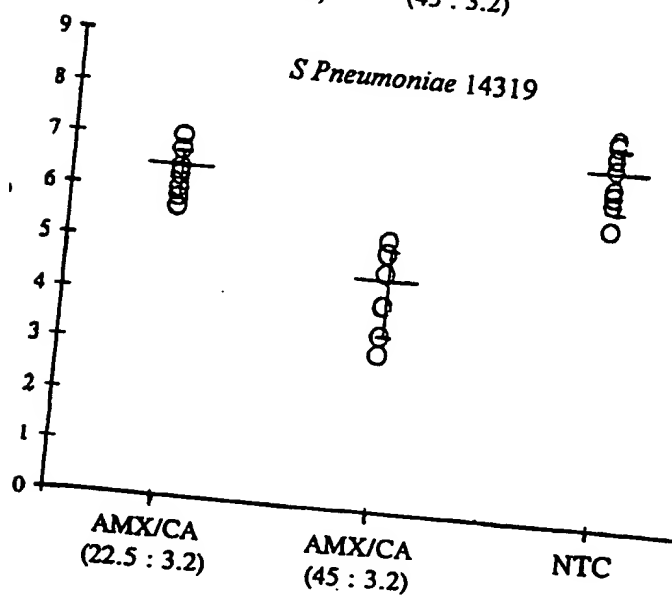


Fig. 2

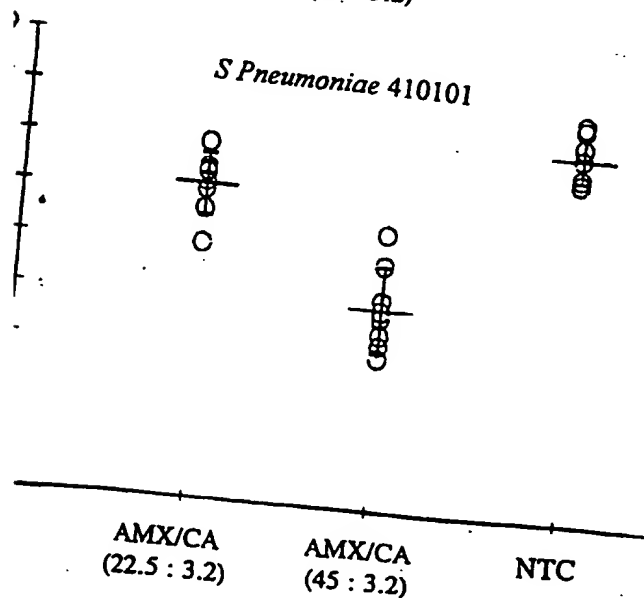


Fig. 3

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/14554

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/43, 31/395

US CL :514/197, 210

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/197, 210

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,525,352 A (COLE ET AL.) 25 June 1985, column 1, lines 28-63, column 7, lines 61-65 and column 9, lines 5-11 and 27-37.	1-4 and 10 ----- 11-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

16 OCTOBER 1996

Date of mailing of the international search report

06 NOV 1996

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Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

RAYMOND J. HENLEY III

Telephone No. (703) 308-1235

*Jap for*

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/14554

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-9  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.